

### **REMARKS**

Applicants have resubmitted this Amendment in response to the Notice of Non-Compliant Amendment and corrected the extra claim 37. Applicants respectfully request that the Amendment be entered of record for the above-identified patent application.

Claims 1-4, 11-13, 21, 28, 32, 34, 37-40, 42, 43, 47, 48, 83, 84, 86, 100 and 101 are pending in this application. Claims 5-10, 14-20, 22-31, 33, 35, 36, 41, 44-46, 49-82, 85 and 87-99 have been withdrawn by the Examiner as being drawn to a non-elected invention.

Applicants respectfully disagree with the statement at page 2 of the Office Action that the election was made without traverse. Applicants' response clearly stated that the elections were made with traverse and that there was no undue burden on the Examiner to search the subject matter of Groups I and II.

At page 3 of the Office Action, claims 100-101 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of copending U.S. Patent Application No. 10/057,646. For brevity, reference is made to page 3 of the Office Action for the complete reasons for rejection.

While Applicants respectfully disagree with and traverse this rejection, a terminal disclaimer is submitted with this response to terminally disclaim the terminal part of the statutory term of any patent granted on the present application that would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. § 154 to 156 and 173 of U.S. Patent Application No. 10/057,646, subject to the conditions noted in the terminal disclaimer.

Accordingly, Applicants respectfully request that the Terminal Disclaimer be entered of record and the rejection of claims 100-101 under the judicially created doctrine of obviousness-type double patenting be reconsidered and withdrawn.

At pages 4-5 of the Office Action, claims 37, 48 and 86 have been rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with the enablement requirement for use of the term "preventing" vascular disease.

For brevity, reference is made to page 4-5 of the Office Action for the complete reasons for rejection.

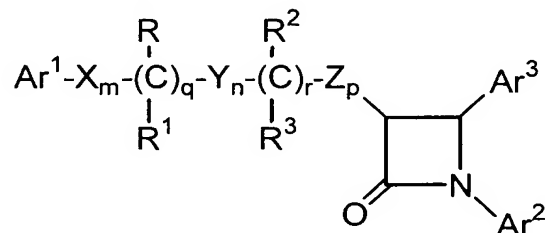
Applicants respectfully assert that the disclosure at page 65, lines 15-20 and knowledge of one of ordinary skill in the art are sufficient to enable one of ordinary skill in the art to understand and make and/or use the claimed invention for preventing vascular disease. While Applicants respectfully disagree with and traverse this rejection, claims 37, 48 and 86 have been amended to delete the phrase "or prevention" to expedite examination of this application, without prejudice to the filing of one or more divisional applications directed to the deleted subject matter.

At pages 5-10 of the Office Action, claims 1-4, 11-13, 37-40, 42, 43, 47-48, 83-84 and 86 have been rejected under 35 U.S.C. §103(a) as obvious over U.S. Patent No. 5,846,966 ("Rosenblum et al.") and The Medical Letter on Drugs and Therapeutics (1998) 40:1030: 68-69 ("Medical Letter"). Claims 21, 28, 32 and 34 were rejected under 35 U.S.C. §103(a) as obvious over Rosenblum et al. and the Medical Letter, further in view of Basic & Clinical Pharma., 6<sup>th</sup> Ed. (1995) 529 ("Katzung"). Claims 100 and 101 were rejected under 35 U.S.C. §103(a) as obvious over Rosenblum et al. Basic & Clinical Pharma., 6<sup>th</sup> Ed. (1995) 529 ("Katzung").

Applicants respectfully traverse these rejections and request that the rejections be reconsidered and withdrawn.

In one embodiment set forth in claim 1, Applicants have discovered a composition comprising:

- (a) at least one peroxisome proliferator-activated receptor (PPAR) activator; and
- (b) at least one sterol absorption inhibitor represented by Formula (I):

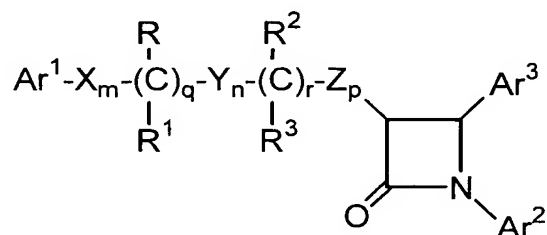


(I)

or isomers thereof, or pharmaceutically acceptable salts, solvates or prodrugs thereof (see original claim 1 for moiety definitions). See original claim 1 and page 3, line 6 - page 4, line 17 of the specification.

In another embodiment set forth in Claim 37, Applicants have discovered a therapeutic combination comprising:

- (a) a first amount of at least one peroxisome proliferator-activated receptor activator; and
- (b) a second amount of at least one sterol absorption inhibitor represented by Formula (I):

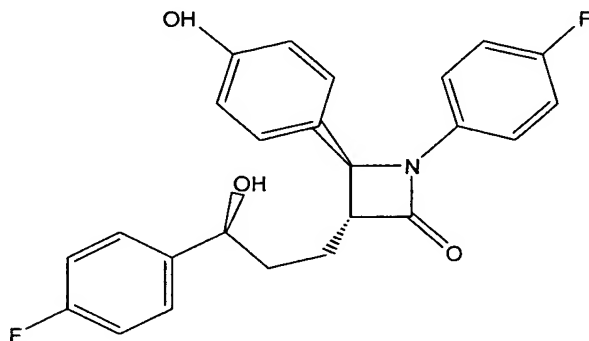


(I)

or isomers thereof, or pharmaceutically acceptable salts, solvates or prodrugs thereof (see original claim 37 for moiety definitions). See original claim 37 and page 21, line 27 - page 22, line 7 of the specification.

In another embodiment set forth in Claim 42, Applicants have discovered a composition comprising:

- (a) at least one fibric acid derivative; and
- (b) a compound represented by Formula (II) below:



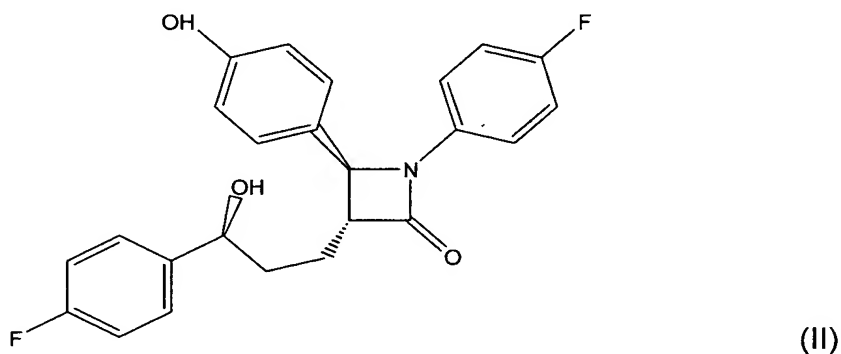
(II)

or pharmaceutically acceptable salt or solvate thereof, or prodrug of the compound of Formula (II) or of the salt or solvate thereof. See original claim 42 and page 4, lines 18-22 of the specification.

In another embodiment set forth in Claim 48, Applicants have discovered a therapeutic combination comprising:

- (a) a first amount of at least one fibric acid derivative; and
- (b) a second amount of a compound represented by Formula (II)

below:

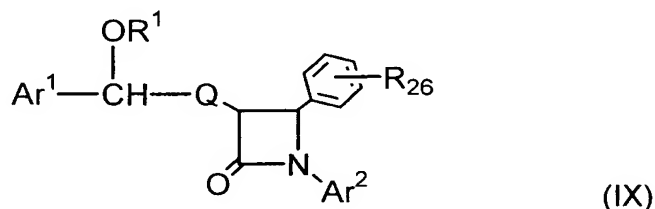


or pharmaceutically acceptable salt or solvate thereof, or prodrug of the compound of Formula (II) or of the salt or solvate thereof, wherein the first amount and the second amount together comprise a therapeutically effective amount for the treatment or prevention of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal. See original claim 48 and page 4, lines 18-22 of the specification.

In another embodiment set forth in Claim 83, Applicants have discovered a composition comprising:

- (a) at least one peroxisome proliferator-activated receptor activator;
- and
- (b) at least one sterol absorption inhibitor represented by Formula

(IX):

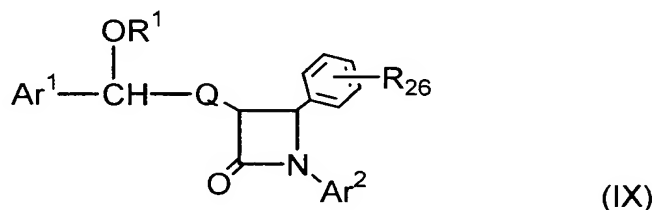


or isomers thereof, or pharmaceutically acceptable salts, solvates or prodrugs thereof (see original claim 83 for moiety definitions). See original claim 83 and page 18, line 24 - page 21, line 26 of the specification.

In another embodiment set forth in Claim 86, Applicants have discovered a therapeutic combination comprising:

(a) a first amount of at least one peroxisome proliferator-activated receptor activator; and

(b) a second amount of at least one sterol absorption inhibitor represented by Formula (IX):



or isomers thereof, or pharmaceutically acceptable salts, solvates or prodrugs thereof, wherein the first amount and the second amount together comprise a therapeutically effective amount for the treatment or prevention of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal. (see original claim 86 for moiety definitions). See original claim 86 and page 4, lines 18-22 of the specification.

In another embodiment set forth in Claim 100, Applicants have discovered a composition comprising (a) at least one antioxidant or vitamin and (b) at least one substituted azetidinone compound or substituted  $\beta$ -lactam compound or isomers thereof, pharmaceutically acceptable salts or solvates, or prodrugs thereof. See original claim 100 at page 162, lines 1-7 of the specification.

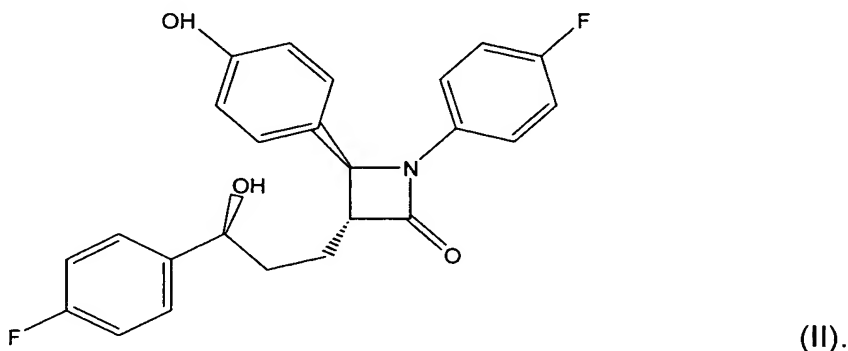
In another embodiment set forth in Claim 101, Applicants have discovered a therapeutic combination comprising (a) a first amount of at least one antioxidant or vitamin and (b) a second amount of at least one substituted azetidinone compound or substituted  $\beta$ -lactam compound or isomers thereof, or pharmaceutically acceptable salts or solvates of the at least one substituted azetidinone compound or the at least one substituted  $\beta$ -lactam compound

compound or isomers thereof, pharmaceutically acceptable salts or solvates, or prodrugs thereof, wherein the first amount and the second amount together comprise a therapeutically effective amount for the treatment of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal. See original claim 101 at page 162, lines 7-18 of the specification.

In the Office Action of July 2, 2003, Applicants were required to elect a species of peroxisome proliferator-activated receptor (PPAR) activator, sterol absorption inhibitor, and third therapeutic agent.

Applicants provisionally elected with traverse fenofibrate as the PPAR activator. See Response to Restriction Requirement and Election of Species of August 1, 2003 ("Response") at page 2, lines 8-9.

Applicants provisionally elected with traverse ezetimibe as the sterol absorption inhibitor, represented by Formula (II) below:



Ezetimibe is the active ingredient in ZETIA™ (ezetimibe) pharmaceutical formulation and VYTORIN™ (ezetimibe/simvastatin) pharmaceutical formulation, both of which are commercially available from MSP (Merck Schering-Plough) Pharmaceuticals, Inc. See Response to Restriction Requirement and Election of Species of August 1, 2003 ("Response") at page 2, lines 12-13.

In the same Response, Applicants provisionally elected niacin as the third therapeutic agent. See Response to Restriction Requirement and Election of Species of August 1, 2003 ("Response") at page 2, lines 15-16.

The claimed compositions and combinations can be useful for treating vascular conditions, diabetes, obesity and/or lowering concentration of a sterol in plasma in a mammal (page 22, lines 8-15 of the specification).

I. The Required *Prima Facie* Case of Obviousness Under 35 U.S.C. § 103 Over US 5,846,966 ("Rosenblum et al.") and The Medical Letter on Drugs and Therapeutics (1998) 40:1030: 68-69 ("Medical Letter") has Failed to be Established

A. The Rejection

Claims 1-4, 11-13, 37-40, 42, 43, 47-48, 83-84 and 86 have been rejected under 35 U.S.C. §103(a) as obvious over US 5,846,966 ("Rosenblum et al.") and The Medical Letter on Drugs and Therapeutics (1998) 40:1030: 68-69 ("Medical Letter").

The reasons for rejection are set forth in the Office Action of May 11, 2005 ("Office Action"), summarized as follows:

Rosenblum et al. disclose that the elected compound of Formula II, ezetimibe, is useful for reducing cholesterol and the risk of atherosclerosis (Office Action at page 6). Medical Letter teaches fenofibrate as useful in reducing serum cholesterol (Office Action at page 6).

It is acknowledged that the primary references do not expressly teach the claimed composition comprising ezetimibe and fenofibrate (Office Action at page 6).

It is alleged that it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine ezetimibe and fenofibrate, since the cited prior art teaches that both ezetimibe and fenofibrate are useful in reducing serum cholesterol individually, citing *In re Kerkoven*, 205 U.S.P.Q. 1069 (Office Action at pages 6-7).

B. The Prior Art

Rosenblum et al. disclose the compound of Formula II (Page 29, Ex. 6). Rosenblum et al. disclose starch-based pharmaceutical compositions including compounds of Formula I of Rosenblum et al. (Ex. A and B Page 29). Rosenblum et al. teach that the active compounds therein can be combined

with HMG CoA reductase inhibitors, such as simvastatin (Page 5, paragraph 0028). Rosenblum et al. also disclose that the active compounds are useful for reducing cholesterol and the risk of atherosclerosis (claims).

Medical Letter teaches fenofibrate as useful in reducing VLDL cholesterol and triglycerides (Medical Letter at page 68).

C. The Required Prima Facie Case of Obviousness Under  
35 U.S.C. § 103 Has Not Been Established

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When making a rejection under 35 U.S.C. § 103, the Examiner has the burden of establishing a prima facie case of obviousness. In re Fritch, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992).

The Examiner can satisfy this burden only by showing an objective teaching in the prior art, or knowledge generally available to one of ordinary skill in the art, which would lead an individual to combine the relevant teachings of the references [and/or the knowledge] in the manner suggested by the Examiner. Id.; In re Fine, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988).

The mere fact that the prior art could be modified does not make the modification obvious *unless the prior art suggests the desirability of the modification* (emphasis added). In re Fritch, 23 U.S.P.Q.2d at 1784; In re Laskowski, 10 U.S.P.Q.2d 1397, 1398 (Fed. Cir. 1989); In re Gordon, 221 U.S.P.Q. 1125, 1127 (Fed. Cir. 1984).

"The ultimate determination of patentability must be based on consideration of the entire record, by a preponderance of evidence, with due consideration to the persuasiveness of any arguments and any secondary evidence." Manual of Patent Examining Procedure, (Rev. 1, Feb. 2003) § 716.01(d) and In re Oetiker, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992).

Claims 1-4, 11-13, 37-40, 42, 43, 47, 48, 83, 84 and 86

Claims 1 and 37 recite a composition and therapeutic combination, respectively, comprising a sterol absorption inhibitor of Formula I shown above, isomers, prodrugs, or pharmaceutically acceptable salts or solvates thereof; and at least one PPAR activator.



Claims 2 and 38 depend from claims 1 and 37, respectively, and recite that the at least one PPAR activator is a fibric acid derivative.

Claim 3 depends from claim 2 and recites that the fibric acid derivative is selected from, *inter alia*, fenofibrate. Claim 4 depends from claim 3 and recites that the fibric acid derivative is fenofibrate.

Claim 13 depends from claim 1 and recites that the amount of sterol absorption inhibitor administered to a mammal ranges from about 0.1 to about 1000 mg/day.

Claim 39 depends from claim 37 and recites that the PPAR activator is administered concomitantly with the sterol absorption inhibitor.

Claim 40 depends from claim 37 and recites that the PPAR activator and the sterol absorption inhibitor are present in separate treatment compositions.

Claims 42 and 48 recite a composition and therapeutic combination, respectively, comprising ezetimibe and at least one fibric acid derivative.

Claim 43 depends from claim 42 and recites that the fibric acid derivative is fenofibrate.

Claim 47 recites a pharmaceutical composition for the treatment of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal using the composition of claim 42 and carrier.

Claims 83 and 86 recite a composition and therapeutic combination, respectively, comprising a sterol absorption inhibitor of Formula IX shown above, isomers, prodrugs, or pharmaceutically acceptable salts or solvates thereof; and at least one PPAR activator.

Claim 84 pharmaceutical composition for the treatment of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal using the composition of claim 83 and carrier.

It is respectfully submitted that the combination of the references cited as rendering the claimed invention obvious is improper because there is no suggestion in the cited references to combine the claimed components of sterol absorption inhibitor (such as that of Formula (I) (e.g., ezetimibe)) and PPAR activator (such as fenofibrate).

Neither Rosenblum et al. nor Medical Letter provides motivation for substituting a PPAR activator for the statin used in combination with ezetimibe described in Rosenblum et al. As disclosed in the Medical Letter Clinical Study section at page 68, fenofibrate is not as effective as statins in lowering LDL cholesterol, a major risk factor in atherogenesis. Since statins are more effective in lowering LDL cholesterol, there is no motivation to substitute a PPAR activator such as fenofibrate for the statin in the combination disclosed in Rosenblum et al.

There is no guidance provided by Rosenblum et al. nor Medical Letter to pick and choose among numerous cholesterol treatments to select the particularly claimed combination of sterol absorption inhibitor (such as that of Formula (II) (e.g., ezetimibe)) and PPAR activator (such as fenofibrate).

Therefore, the prima facie case of obviousness based upon Rosenblum et al. and Medical Letter has not been established and the rejection of claims 1-4, 11-13, 37-40, 42, 43, 47, 48, 83, 84 and 86 should be reconsidered and withdrawn.

II. The Required Prima Facie Case of Obviousness Under 35 U.S.C. § 103 Over US 5,846,966 ("Rosenblum et al.") and The Medical Letter on Drugs and Therapeutics (1998) 40:1030: 68-69 ("Medical Letter"), further in view of Basic & Clinical Pharma., 6<sup>th</sup> Ed. (1995) 529 ("Katzung") has Failed to be Established

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A. The Rejection

Claims 21, 28, 32 and 34 were rejected under 35 U.S.C. §103(a) as obvious over Rosenblum et al. and the Medical Letter, further in view of Basic & Clinical Pharma., 6<sup>th</sup> Ed. (1995) 529 ("Katzung").

The reasons for rejection are set forth in the Office Action, summarized as follows:

Rosenblum et al. and Medical Letter suggest a composition containing fenofibrate and ezetimibe (Office Action at page 7).

It is acknowledged that the primary references do not expressly teach the claimed composition containing niacin (Office Action at page 7).

Katzung teaches niacin as useful for lowering cholesterol (Office Action at page 7).

It is alleged that it would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate niacin into the ezetimibe and fenofibrate composition, since the cited prior art teaches that all three ingredients are useful in reducing serum cholesterol, citing *In re Kerkoven*, 205 U.S.P.Q. 1069 (Office Action at pages 7-8).

B. The Prior Art

Rosenblum et al. disclose the compound of Formula II (Page 29, Ex. 6). Rosenblum et al. disclose starch-based pharmaceutical compositions including compounds of Formula I of Rosenblum et al. (Ex. A and B Page 29). Rosenblum et al. teach that the active compounds therein can be combined with HMG CoA reductase inhibitors, such as simvastatin (Page 5, paragraph 0028). Rosenblum et al. also disclose that the active compounds are useful for reducing cholesterol and the risk of atherosclerosis (claims). Rosenblum et al. do not disclose niacin.

Medical Letter teaches fenofibrate as useful in reducing VLDL cholesterol and triglycerides (Medical Letter at page 68). Medical Letter discloses that niacin is a drug for treating hypertriglyceridemia (Medical Letter at page 69). Medical Letter does not suggest or disclose a combination of substituted azetidinone compound, PPAR activator and niacin.

Katzung discloses that niacin decreases VLDL and LDL levels in patients (Katzung at 529). Katzung does not suggest or disclose a combination of substituted azetidinone compound, PPAR activator and niacin.

C. The Required Prima Facie Case of Obviousness Under 35 U.S.C. § 103 Has Not Been Established

Claim 21 depends from claim 1 and recite that the composition further comprises nicotinic acid, niceritrol, nicofuranose or acipimox. Claim 28 depends from claim 1 and recites that the composition further comprises at least one antioxidant or vitamin. Thus the composition would comprise sterol

absorption inhibitor, PPAR activator such as fenofibrate, and niacin, for example.

Claim 32 depends from claim 1 and recites that the composition further comprises at least one cardiovascular agent selected from the group consisting of calcium channel blockers, adrenergic blockers, adrenergic stimulants, angiotensin converting enzyme (ACE) inhibitors, antihypertensive, angiotensin II receptor antagonists, anti-anginal agents, coronary vasodilators, diuretics and combinations thereof.

Claim 34 recites a pharmaceutical composition for the treatment of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal using the composition of claim 1 and carrier. Claim 34 does not require the presence of nicotinic acid, niceritrol, nicofuranose or acipimox, although such compounds could be present.

With respect to claims 21 and 28, Rosenblum et al. nor Medical Letter, taken alone or together as suggested in the Office Action, provides any motivation for a triple combination treatment of sterol absorption inhibitor (such as that of Formula (II) (e.g., ezetimibe)), PPAR activator (such as fenofibrate) and niacin. These references provide no guidance or motivation as to the desirability for such as combination or selecting the particular components of the combination, or the potential effect of drug-drug interactions. For example, in the Drug Interaction section at page 69, Medical Letter discloses that it is unclear whether, *like gemfibrozil and niacin*, concurrent administration of fenofibrate with a statin could increase the risk of rhabdomyolysis. In the Advisory Action of December 7, 2004, the Examiner encouraged Applicants to bring forth evidence of potential drug-drug interaction. This evidence is present in the Drug Interaction section at page 69 of Medical Letter cited in the rejection as pointed out above and the burden therefore is shifted to the Examiner to refute the teaching in the reference which was cited in the rejection.

Katzung provides no further incentive to one skilled in the art to include niacin in a composition or therapeutic combination of sterol absorption inhibitor and PPAR activator.

Because of the difference of the way that each component of the presently claimed combination acts, it is respectfully submitted that the rejection is based upon an improper combination of references.

With respect to claim 32, Rosenblum et al., Medical Letter, nor Katzung, taken alone or together as suggested in the Office Action, provides any motivation for a triple combination treatment of sterol absorption inhibitor (such as that of Formula (II) (e.g., ezetimibe)), PPAR activator (such as fenofibrate) and at least one cardiovascular agent selected from the group consisting of calcium channel blockers, adrenergic blockers, adrenergic stimulants, angiotensin converting enzyme (ACE) inhibitors, antihypertensive, angiotensin II receptor antagonists, anti-anginal agents, coronary vasodilators, diuretics and combinations thereof.

With respect to claim 34, Rosenblum et al., Medical Letter, nor Katzung, taken alone or together as suggested in the Office Action, provides any motivation for a pharmaceutical composition for the treatment of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal using the composition of claim 1 and carrier. Claim 34 does not require the presence of nicotinic acid, niceritrol, nicofuranose or acipimox, although such compounds could be present.

Therefore, the prima facie case of obviousness based upon Rosenblum et al., Medical Letter and Katzung has not been established and the rejection of claims 21, 28, 32 and 34 should be reconsidered and withdrawn.

III. The Required *Prima Facie* Case of Obviousness Under 35 U.S.C. § 103 Over US 5,846,966 ("Rosenblum et al.") and Basic & Clinical Pharma., 6<sup>th</sup> Ed. (1995) 529 ("Katzung") has Failed to be Established

A. The Rejection

Claims 100 and 101 were rejected under 35 U.S.C. §103(a) as obvious over Rosenblum et al. and Basic & Clinical Pharma., 6<sup>th</sup> Ed. (1995) 529 ("Katzung").

The reasons for rejection are set forth in the Office Action, summarized as follows:

Rosenblum et al. teaches that ezetimibe is useful for reducing cholesterol and the risk of atherosclerosis (Office Action at page 8).

Katzung teaches niacin as useful for lowering cholesterol (Office Action at page 8).

It is acknowledged that the primary references do not expressly teach the claimed composition containing niacin (Office Action at page 8).

It is alleged that it would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate niacin into the ezetimibe composition, since the cited prior art teaches that both ingredients are useful in reducing serum cholesterol, citing *In re Kerkoven*, 205 U.S.P.Q. 1069 (Office Action at page 8).

B. The Prior Art

Rosenblum et al. disclose the compound of Formula II (Page 29, Ex. 6). Rosenblum et al. disclose starch-based pharmaceutical compositions including compounds of Formula I of Rosenblum et al. (Ex. A and B Page 29). Rosenblum et al. teach that the active compounds therein can be combined with HMG CoA reductase inhibitors, such as simvastatin (Page 5, paragraph 0028). Rosenblum et al. also disclose that the active compounds are useful for reducing cholesterol and the risk of atherosclerosis (claims). Rosenblum et al. do not disclose niacin.

Katzung discloses that niacin decreases VLDL and LDL levels in patients (Katzung at 529). Katzung does not suggest or disclose a combination of substituted azetidinone compound and niacin.

C. The Required Prima Facie Case of Obviousness Under 35 U.S.C. § 103 Has Not Been Established

Claims 100 and 101

Claims 100 and 101 recite a composition or therapeutic combination comprising (a) at least one antioxidant or vitamin and (b) at least one substituted azetidinone compound or substituted  $\beta$ -lactam compound or isomers, prodrugs, salts or solvates thereof.

With respect to patentability of the composition or combination of Claims 100 and 101, neither Rosenblum nor Katzung suggests or disclose combinations of a sterol absorption inhibitor and antioxidant or vitamin.

Therefore, the prima facie case of obviousness based upon Rosenblum et al. and Katzung has not been established and the rejection of claims 100 and 101 should be reconsidered and withdrawn.

Accordingly, Applicants respectfully request that the § 103(a) rejections of claims 1-4, 11-13, 21, 28, 32, 34, 37-40, 42, 43, 47-48, 83, 84, 86 and 100-101 be reconsidered and withdrawn.

Respectfully submitted,

Date: September 8, 2005



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